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Stress (Takotsubo) cardiomyopathy—a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning

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SUMMARY

Stress cardiomyopathy, also referred to as Takotsubo cardiomyopathy, is an increasingly recognized clinical syndrome characterized by acute reversible apical ventricular dysfunction. We hypothesize that stress cardiomyopathy is a form of myocardial stunning, but with different cellular mechanisms to those seen during transient episodes of ischemia secondary to coronary stenoses. In this syndrome, we believe that high levels of circulating epinephrine trigger a switch in intracellular signal trafficking in ventricular cardiomyocytes, from G_s protein to G_i protein signaling via the β_2-adrenoceptor. Although this switch to β_2-adrenoceptor–G_i protein signaling protects against the proapoptotic effects of intense activation of β_1-adrenoceptors, it is also negatively inotropic. This effect is greatest at the apical myocardium, in which the β-adrenoceptor density is greatest. Our hypothesis has implications for the use of drugs or devices in the treatment of patients with stress cardiomyopathy.

KEYWORDS β_2-adrenoceptor, epinephrine, Gi protein, stress cardiomyopathy, Takotsubo cardiomyopathy

REVIEW CRITERIA

A comprehensive search of the MEDLINE database from 1965 to 1 July 2007 was performed. Search terms included "stress cardiomyopathy", "Takotsubo", "Tako-tsubo", "ampulla-shaped cardiomyopathy" and "apical ballooning". Additionally, the citation sections of retrieved articles were reviewed to identify additional relevant articles. For inclusion, a paper had to be full text. If articles were not published in English, only the abstract was used as a data source.

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Learning objectives

Upon completion of this activity, participants should be able to:

1 Describe the primary pathophysiology of stress cardiomyopathy.
2 Identify the clinical presentations of stress cardiomyopathy.
3 List the most likely triggers of stress cardiomyopathy.
4 Describe the mechanisms contributing to the effects of stress cardiomyopathy.
5 Describe appropriate management strategies for acute stress cardiomyopathy.

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INTRODUCTION

In the 16 years since the first report by Satoh *et al.*,[1] the entity of stress cardiomyopathy (also termed Takotsubo cardiomyopathy, transient left ventricular apical ballooning syndrome, or ampulla-shaped cardiomyopathy) has been increasingly recognized. More than 300 articles on the topic have been published, the majority in the last 5 years. Despite this increased awareness, the pathophysiology of the condition remains unknown, and few reports have suggested a specific mechanism, beyond high catecholamine levels, as a trigger for the syndrome. Here, we review the clinical syndrome and suggest a novel pathophysiological explanation that focuses on the direct effects of high epinephrine levels on the ventricular myocardium. The syndrome represents a form of epinephrine-mediated acute myocardial stunning, with a predilection for the apical myocardium.

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THE CLINICAL SYNDROME

The characteristic clinical syndrome of stress cardiomyopathy is acute left ventricular dysfunction, usually after a sudden emotional or physical stress. Patients typically present with cardiac chest pain, which can mimic an acute coronary syndrome. Although the coronary arteries have no flow-limiting lesions, acute changes on the electrocardiogram, suggesting ischemia, and raised levels of cardiac enzymes, reflecting acute myocardial injury, are usually present. Left ventricular dysfunction and wall-motion abnormalities are typically seen, affecting the apical and, frequently, the midventricular myocardium, but sparing the basal myocardium. On left ventriculography, echocardiography or cardiac MRI, these functional abnormalities typically resemble a flask with a short, narrow neck and wide, rounded body (Figure 1; cardiac MRI movies recorded during the acute phase and follow-up period, respectively, are provided as Supplementary Movies 1 and 2 online). The shape of the ventricle at end systole resembles the Japanese fisherman's octopus pot—the tako-tsubo—from which the syndrome derives its original name. The hypercontractile basal myocardium can generate left ventricular outflow tract obstruction in the presence of apical and midwall hypokinesis. The final element of the syndrome is that left ventricular function and apical wall motion return to normal within days or weeks of the acute insult, in a similar manner to traditional myocardial stunning, providing no further acute cardiac events occur.[2]

The long-term prognosis of patients with this syndrome is excellent. In one series of 13 cases, all patients who survived the acute event ($n=12$) were alive at 5-year follow-up.[3] A clinical series from the US[4] and a detailed systematic review of case reports and cohort studies[5] have recently been reported. In 2006, the syndrome was renamed stress cardiomyopathy and reclassified within the subgroup of acquired cardiomyopathies.[6]

THE TRIGGERING EVENT

The common etiologic feature of stress cardiomyopathy is sudden physical or emotional stress as the precipitant. Two reports demonstrated an increased incidence of the syndrome after earthquakes in Japan.[7,8] The condition has also been reported in patients undergoing noncardiac surgery[9,10] and in patients with noncardiac medical emergencies.[11–15] If measured early after the triggering event, a substantial increase in plasma catecholamine levels is reported in many patients following stress cardiomyopathy. Serum catecholamine levels are not usually measured in routine clinical practice, but, when measured, the catecholamine levels seen in this syndrome are significantly higher than those found in conditions such as acute myocardial infarction or cardiac failure and up to 34 times higher than normal resting values.[16,17] This issue is still a subject of debate, however, because the plasma half-life of epinephrine is approximately 3 min,[18] and most patients present to emergency departments at least 30 min (>10 half-lives), and in some cases several hours, after symptom onset. The peak epinephrine level to which the myocardium is exposed at the point of stress will, therefore, be several logfold higher than any measurement of serum epinephrine level taken on admission to an emergency department, which could have returned to basal levels after the delay in presentation.

The surge in catecholamine levels results in cardiac dysfunction similar to that often classified as 'stunning with normal coronary blood flow'. This phenomenon is a relatively common finding in patients with acute intracranial injury, particularly acute subarachnoid hemorrhage, who also have surges in sympathetic activity in response to acute hemorrhage.[19] Approximately 10% of patients with acute intracranial injury have acute ischemic electrocardiographic changes,

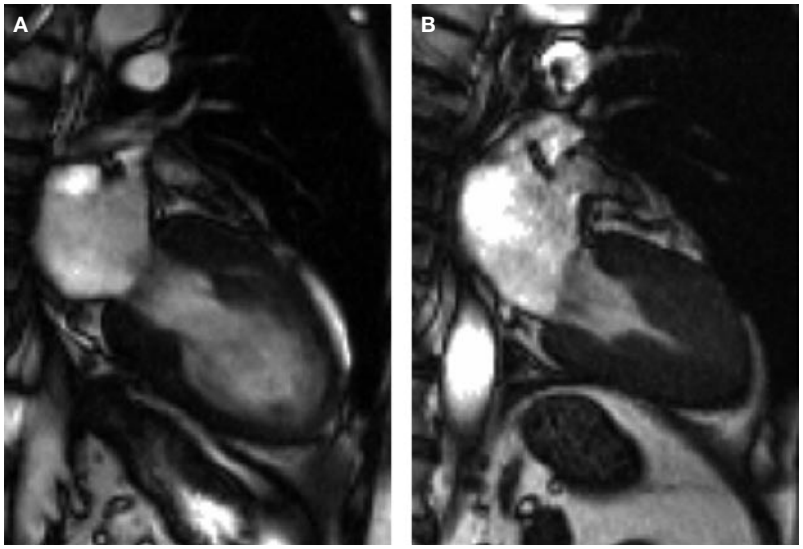

Figure 1 Left ventricular end systolic cardiac MRI. (**A**) Acute phase with akinetic apical and mid-left ventricular wall and reduced or absent wall thickening (a cardiac MRI movie demonstrating the acute phase is provided as Supplementary Movie 1 online). (**B**) Follow-up image at 5 months, demonstrating normal left ventricular systolic function, with recovery of motion and wall thickening in all segments (a movie recorded during follow-up is provided as Supplementary Movie 2 online).

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raised levels of cardiac enzymes, and acute, but reversible, left ventricular impairment, all in the presence of normal coronary arteries.[20–22] The pathology of the myocardium in such patients is similar to that sometimes seen in individuals with stress cardiomyopathy, with leukocyte infiltration and contraction-band necrosis.[23] The acute clinical instability during the early phase of a major neurological event means that optimum myocardial assessment (e.g. angiography, cardiac MRI) is rarely performed until after recovery. The same clinical picture is seen in patients with surges in catecholamine levels secondary to pheochromocytomas.[24,25]

THE HYPOTHESIS

Surges in catecholamine levels are an evolutionary response to sudden shock, fright or danger. Proposed mechanisms for catecholamine-mediated stunning in stress cardiomyopathy include epicardial spasm, microvascular dysfunction, hyperdynamic contractility with mid-ventricular or outflow tract obstruction, and direct effects of catecholamines on cardiomyocytes. We hypothesize that stunning is the result of epinephrine-mediated effects on cardiomyocytes.

Stimulus trafficking

At physiological and elevated concentrations, norepinephrine, released from the sympathetic nerves, acts predominantly via the β_1-adrenoceptors (β_1ARs) on ventricular cardiomyocytes, exerting positive inotropic and lusitropic responses. These effects are the result of β_1AR coupling to the G_s protein family, which increases intracellular cyclic AMP levels through adenyl cyclase. Elevated cyclic AMP concentrations activate protein kinase A (PKA), which phosphorylates several downstream intracellular targets, resulting in an increased contractile response. Epinephrine also binds β_1ARs and activates this response, but it has a higher affinity for the β_2-adrenoceptor (β_2AR). Humans have a higher concentration of β_2ARs in the ventricular myocardium than other mammals. The ratio of β_1ARs:β_2ARs in normal human ventricular myocardium is approximately 4:1.[26] Studies with transgenic mice that overexpress human β_2ARs have enabled the pharmacology of the human β_2AR in the ventricular cardiomyocyte to be studied.[27] At epinephrine concentrations in the normal physiological range, epinephrine binding to β_2ARs activates the G_s protein–adenyl cyclase–PKA pathway, resulting in a positive inotropic response. At higher 'supraphysiological' concentrations, epinephrine stimulates a negative inotropic effect on myocyte contraction.[28] This change in response results from a switch in β_2AR coupling, from G_s protein signaling to G_i protein signaling,[29] a process called stimulus trafficking (Figure 2). PKA-mediated phosphorylation of the β_2AR, resulting from intense activation of the β_1AR–G_s protein and β_2AR–G_s protein pathways, is thought to initiate the switch in signal trafficking from β_2AR–G_s protein to β_2AR–G_i protein coupling.[30,31]

Although the bell-shaped concentration–response curve for the function of epinephrine on the human β_2AR has been demonstrated only in the transgenic mouse model, there is evidence for potential β_2AR–G_i protein interactions in human atrial[32] and ventricular[33] muscle. Stimulation of β_2AR–G_i protein signaling pathways has been shown to produce a negative inotropic effect on human ventricular myocytes,[34] although the effect was much more pronounced in cells from a failing human heart, in which G_i protein signaling is increased, than in cells from a healthy heart.[35] After the surge in epinephrine levels has cleared from the circulation, β_2ARs coupled to G_i proteins either switch back to G_s protein coupling or are internalized and degraded, enabling cardiomyocytes to recover their inotropic function. This sequence of events would explain the reported recovery of ventricular function in individuals with stress cardiomyopathy.

The mechanism of the negative inotropic effect mediated by β_2AR–G_i protein interaction is still under debate. The G_i protein pathway can activate the p38 mitogen-activated protein (MAP) kinase pathway, which exerts a negative inotropic effect.[36–38] Alternatively, β_2AR–G_i protein signaling could upregulate the sodium–calcium ion exchanger,[39] inhibit L-type calcium channel currents[40] or act through other as yet unidentified pathways. At first, these responses seem counterintuitive to the evolutionary need for catecholamine-induced increases in cardiac output. High levels of β_1AR-mediated G_s protein pathway activation induce apoptotic pathways in the cardiomyocyte. The switch to G_i protein signaling via the β_2AR at high epinephrine concentrations might, therefore, have a protective role. β_2AR–G_i protein coupling also activates the phosphoinositide 3 kinase–protein kinase B (Akt) pathway through the $G_i\beta\gamma$ subunit, which has an antiapoptotic effect.[41] This action would

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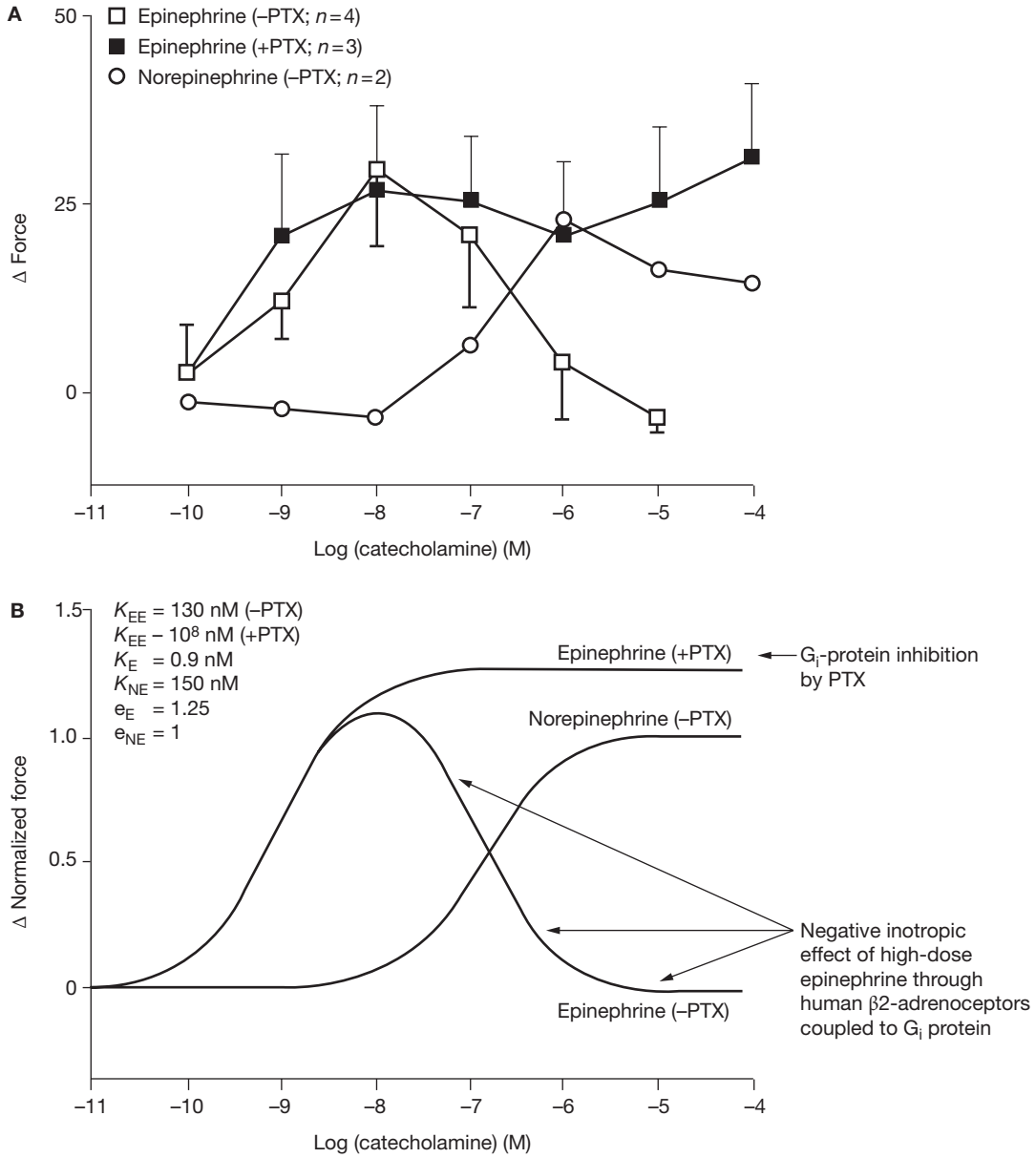

Figure 2 Inotropic effects of epinephrine and norepinephrine. (**A**) Effects of epinephrine and norepinephrine on ventricular myocardium from transgenic mice overexpressing the human β_2-adrenoceptor (TG4 mice), and the effects of PTX. (**B**) Simulations of the ventricular effects of epinephrine and PTX treatment. Abbreviation: PTX, pertussis toxin. Permission obtained from the American Society for Pharmacology and Experimental Therapeutics © Heubach JF *et al*. (2004) *Mol Pharmacol* **65:** 1313–1322.

counteract the proapoptotic effect of excessive β_1AR–G_s protein pathway activation[42] and act as a physiological balance to prevent excessive catecholamine-mediated damage. Patchy apoptosis could still occur before, or despite, the activation of G_i-protein-dependent pathways, explaining the elevation of troponin levels and necrosis seen in patients following stress cardiomyopathy. The scale of myocardial injury is probably reduced compared with the scenario of unopposed activation mediated by β_1AR–G_s protein and β_2AR–G_s protein pathways.

Negative inotropism mediated by epinephrine, β_2AR and G_i protein interactions can explain the propensity for apical suppression with basal sparing in stress cardiomyopathy. Sympathetic stimulation of adrenoceptors in the ventricular myocardium is achieved through two routes: local release of norepinephrine by sympathetic nerve endings, directly innervating the

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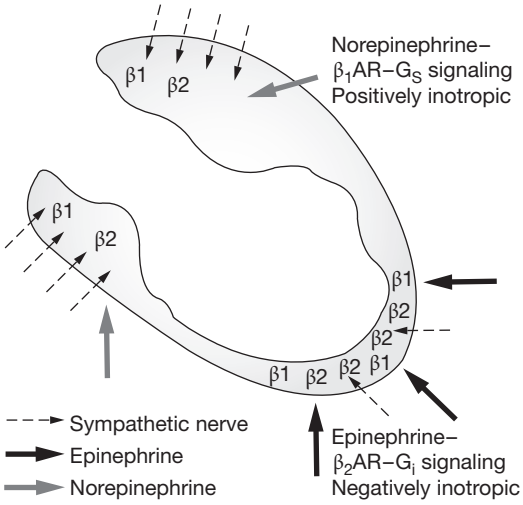

Figure 3 Schematic representation of the regional differences in response to high catecholamine levels, explaining stress cardiomyopathy.

myocardium; and diffusion of circulating catecholamines into the myocardium from the coronary circulation. In normal human hearts, the density of sympathetic nerve endings, as identified by tyrosine hydroxylase during autopsy, is approximately 40% higher in the basal myocardium than in the apical myocardium.[43] Sympathetic innervation of the myocardium in the canine left ventricle shows a similar pattern, with the highest density of nerve endings found at the base, decreasing to the lowest levels at the apex.[44] In the normal physiological setting, the majority of norepinephrine is released from nerve terminals, with circulating norepinephrine released from the adrenal medulla making a minimal contribution. The innervation pattern, therefore, is inconsistent with the region of greatest dysfunction found in stress cardiomyopathy.

Provided that perfusion is balanced, circulating catecholamines have a global effect on the myocardium. The magnitude of the effect will depend on the local density of adrenoceptors in different regions of the myocardium. Mori *et al.* demonstrated that the canine heart has a higher concentration of β-adrenoceptors in the apical myocardium, with the concentration gradient decreasing from apex to base (455 vs 341 fmol/mg protein).[44] This difference in distribution resulted in a greater contractile response to catecholamine challenge in the apical myocardium than in the basal myocardium. The proposed explanation for this difference is that the density of β-adrenoceptors in the apical myocardium is increased to compensate for the decrease in direct sympathetic innervation, to maintain a balanced responsiveness of the ventricle to sympathetic drive. This difference implies that the apex might be more sensitive than the basal myocardium to circulating catecholamines and that, under conditions of stress, the circulating catecholamine is predominantly epinephrine. Mori *et al.* did not, however, differentiate between β_1ARs and β_2ARs in their study, and this greater density of adrenoceptors at the apex has not been assessed in the human ventricle. Their observation is supported by findings from models of heart failure induced by either acute or chronic catecholamine infusion.[45,46] These models demonstrate increased myocardial fibrosis in the apical ventricular myocardium, indicating that the apical myocardium has a raised sensitivity to circulating catecholamines and in particular the β-adrenoceptor agonist isoprenaline used in these studies. An increasing density of β_2ARs from the base to the apex could explain the regional difference in response to high catecholamine levels, with circulating epinephrine having a greater influence on apical, relative to basal, function (Figure 3).

We do not discount the role of norepinephrine in stress cardiomyopathy, given the systemic activation of the sympathetic nervous system in response to sudden shock. Norepinephrine-mediated coronary vasospasm might have an additional role, and there is evidence of coronary or inducible spasm at provocation in some patients.[47] This response is unsurprising following a massive surge in norepinephrine levels, although other investigators have found no evidence of epicardial or microcirculatory flow abnormalities in stress cardiomyopathy.[48] Coronary vasospasm could impose a secondary ischemic insult, superimposed on the primary epinephrine-induced apical stunning.

Sex-related differences in stress cardiomyopathy

Many unanswered questions regarding stress cardiomyopathy remain. One of the most puzzling concerns why there is an apparent increased incidence in females, who comprise over 90% of reported cases. Sex-related differences in the response of the adrenal medulla to sudden high-intensity sympathetic discharge and differing pharmacokinetics of epinephrine release could explain the increased rate in women.

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Of interest, basal plasma epinephrine levels are lower in women than in men.[49] This difference could reflect reduced synthesis, increased degradation or reduced basal release with more potential stores for sudden release. Estrogens have cardioprotective effects against acute injury through a variety of complex mechanisms.[50,51] Stress activates early gene expression in both the central nervous system and the ventricular myocardium in rodent models,[52,53] the myocardial changes in gene expression being mediated by activation of both α-adrenoceptors and β-adrenoceptors. Estrogen reduces these changes in gene expression, protecting against the apical ventricular dysfunction observed in this rodent model of stress cardiomyopathy induced by conscious immobilization.[54] Chronic (but not acute) exposure of the rat ventricular myocardium to estrogen reduces the enhanced expression of β_1ARs that occurs in response to their activation by catecholamines and ischemia–reperfusion injury.[55] Furthermore, oophorectomy increases the expression of β_1ARs, an effect that is reversed by estrogen supplementation.[56] Beyond the myocardium, greater vascular β_2AR-mediated sensitivity has been demonstrated in women than in men.[57] Estrogens could, therefore, influence the β_1AR:β_2AR signaling ratio in women in favor of the protective effects of β_2AR–G_i protein signaling following surges in catecholamine levels. This protection would occur at the mechanical cost of negative inotropism in the regions with the highest density of β-adrenoceptors, namely the apical myocardium. Perhaps men who lack this protective 'dampening' effect on β_1AR–G_s protein signaling develop more-intense acute cardiotoxicity mediated by β_1AR–G_s protein signaling following surges in catecholamine levels, resulting in a fatal event rather than stress cardiomyopathy.

Atypical stress cardiomyopathy

The number of reports of patients with an atypical or 'inverted Takotsubo' pattern of disease is increasing, with basal ventricular suppression, sometimes extending to the midventricular myocardium, but with apical sparing.[22,25,58,59] The mechanism described above is derived from a scenario in which the entire ventricular myocardium is exposed to the same high concentration of circulating epinephrine released from the adrenal medulla. In this scenario, the gradient of the density of β_2ARs explains the predominance of apical suppression. Other factors can also influence the epinephrine concentration in the myocardium, however, and these could account for the different local concentration gradients and phenotypes observed. For example, conversion of norepinephrine to epinephrine by phenylethanolamine *N*-methyltransferase in the ventricular myocardium has been demonstrated in rabbits,[60] and this would occur at points of highest sympathetic innervation.

CLINICAL TESTING

Our hypothesis is readily testable in animal models by use of genetic tools to manipulate the density of β-adrenoceptors and assessment of the ventricular response to catecholamines. Measurement of the gradient of the density of β_2ARs in the human ventricle is more challenging. Direct measurement of the density of β_2ARs in tissue specimens taken from different regions of the human ventricle would be ideal, but obtaining left ventricular biopsies from 'normal' human hearts raises major ethical concerns, and 'normal' donor hearts unsuitable for transplantation have frequently been exposed to high catecholamine levels before explantation. An alternative is *in vivo* measurement with PET and labeled receptor ligands.[61] *In vivo* or tissue measurements of β_1AR:β_2AR ratios in cardiomyocytes can also be confounded by β_2ARs on the coronary vasculature[62] and on cardiac fibroblasts.[63]

CLINICAL IMPLICATIONS

This pathophysiological hypothesis might enable improved management of patients in the acute phase of stress cardiomyopathy. Whereas some patients require only supportive therapy, others can present with acute cardiogenic shock, necessitating admission to intensive care for hemodynamic support. Epinephrine has a causative role in stress cardiomyopathy and the deterioration of myocardial function, and additional 'therapeutic' epinephrine might drive further β_2AR–G_i-protein-mediated negative inotropism. The use of inotropic agents, particularly dobutamine, in patients with stress cardiomyopathy and cardiogenic shock, therefore, seems counterintuitive. Some β-blockers can also cause stimulus trafficking of β_2ARs to G_i protein coupling,[64] which suggests that use of these agents in patients with stress cardiomyopathy might be inappropriate, despite the high catecholamine levels. Aortic balloon

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pump counterpulsation might be the best first-line hemodynamic support, with intravenous calcium or levosimendan, the calcium-sensitizing agent, as second-line pharmacological support. In cases of life-threatening acute left ventricular failure, temporary mechanical support with a left ventricular assist device can be indicated. Ventricular support could provide time for the ventricular myocardium to recover, as observed in the natural history of stress cardiomyopathy. We must highlight, however, that these proposals are founded on a hypothesis and require a clinical study for validation.

CONCLUSIONS

In summary, we hypothesize that stress cardiomyopathy is a form of myocardial stunning, but with cellular mechanisms different to those caused by transient episodes of ischemia secondary to coronary stenoses. High levels of circulating epinephrine trigger a switch in intracellular signal trafficking, from G_s protein to G_i protein signaling through the β_2AR. This change in signaling is negatively inotropic, and the effect is greatest at the apical myocardium, in which the density of β-adrenoceptors is highest. This hypothesis has implications for the use of drugs or devices in the treatment of patients with stress cardiomyopathy.

Supplementary information in the form of two movies is available on the *Nature Clinical Practice Cardiovascular Medicine* website.

KEY POINTS

- Stress cardiomyopathy is the result of the direct effects of high levels of epinephrine on the ventricular myocardium
- High levels of epinephrine are negatively inotropic; they switch β2-adrenoceptor coupling in ventricular cardiomyocytes, from the Gs protein to the Gi protein signaling pathway
- The density of β-adrenoceptors is greatest at the apical myocardium of the mammalian heart, which explains the regional nature of the stunning in response to high levels of circulating epinephrine after stressful stimuli
- This effect is reversible after the epinephrine levels return to normal, which explains why left ventricular function and apical wall motion return to normal within days to weeks of the acute insult

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